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Abstract

Pediatric anxiety disorders have high prevalence rates and morbidity and are associated with considerable functional impairment and distress. They may be predictors for the development of other psychiatric disorders and, without intervention, are more likely to persist into adulthood. While evidence-based pharmacological and behavioral interventions are currently available, there remains a sizable subset of youth who remain only partially treatment-responsive and therefore symptomatic following treatment. Novel methods of treatment, pharmacologic and non-pharmacologic, including acceptance and commitment therapy (ACT), attention bias modification (ABM), d-cycloserine (DCS) augmentation of cognitive behavioral treatment (CBT), and glutamatergic agents such as riluzole, are briefly introduced and discussed.

Introduction and context

Anxiety disorders in the pediatric population occur frequently, with prevalence rates of 10% to 20% [1,2]. While developmentally appropriate worry and fear are common in children and adolescents, clinically significant levels of anxiety can be chronic and disabling [3]. Pediatric anxiety disorders have high levels of comorbidity with other anxiety disorders, depression, and disruptive behavior disorders and are associated with significant psychosocial impairment as well as increased likelihood of substance abuse and suicidal behavior [3-8]. When left untreated, anxiety in childhood is a predictor for anxiety disorders and major depression later in life [7].

CBT and selective serotonin reuptake inhibitors (SSRIs) have emerged as the most empirically robust treatment modalities for pediatric anxiety disorders [9]. Monotherapy and combination therapy (SSRIs + CBT) have been demonstrated to be efficacious in large comparative trials; one multisite study reported treatment response rates of 81% for sertraline + CBT combination therapy, 60% for CBT monotherapy, and 55% for sertraline monotherapy, relative to a 24% response rate for placebo [10]. While CBT and SSRIs are considered first-line treatment for youth with anxiety, up to 50% continue to meet criteria for anxiety disorder after treatment [1,2,11]. For this reason, research has sought methods both to augment currently available treatments as well as to develop alternative modalities to treat pediatric anxiety disorders. This report presents emerging evidence for new treatment methods that have shown promising results as potential interventions for youth with anxiety disorders (Table 1).

Non-pharmacological interventions

Acceptance and commitment therapy

The extant literature regarding ACT has demonstrated empirical efficacy. Favorable results in adult trials [12,13] have spurred discussion regarding the application and utility of ACT for the treatment of pediatric anxiety disorders. Whereas CBT focuses on the content of cognitions and seeks to alter these thoughts, ACT is concerned about the process and function of thoughts in specific contexts [14,15]. ACT seeks to increase psychological flexibility through cognitive defusion and acceptance [14]. Individuals are encouraged to recognize thoughts as simply thoughts, which are not necessarily rooted in reality or truth [16]. Additionally, experiential

Table 1. Published reports on novel non-pharmacological intervention for anxiety disorders in youth

Targeted symptoms	Treatment	Author	Design	Post-treatment results
Anxiety and obsessive thoughts	ACT	Brown and Hooper [23]	Case study; n = 1; age: 18 years; 17 sessions	Decreased experiential avoidance, increased social confidence, and decreased duration of anxiety episodes
Chronic anxiety	ABM	Bar-Haim *et al.* [31]	RCT; n = 34; ages: 8-14 years; 2 sessions	Reduction in threat bias in ABM group
Separation anxiety, social phobia, specific phobia, and generalized anxiety disorder	ABM	Eldar *et al.* [32]	RCT; n = 40; ages: 8-14 years; 4 sessions	Reduction in threat bias in ABM group; significant reductions in anxiety symptoms in ABM group but no differences in control group
CBT-resistant separation anxiety, social phobia	ABM-adjunctive CBT	Bechor *et al.* [33]	Case series, n = 6; ages: 13-17 years; 8 sessions	Baseline threat bias not uniform in group; significant reductions in child-rated anxiety and parent-rated anxiety

ABM, attention bias modification; ACT, acceptance and commitment therapy; CBT, cognitive behavioral therapy; RCT, randomized controlled trial.

avoidance, which is defined as the avoidance of specific experiences (e.g. thoughts, emotions, and physiological sensations), is considered unproductive and counter to acceptance. Rather than direct symptom reduction, the goal of treatment is to engage in behaviors that will facilitate living a life that reflects the individual's values, and as a side effect of this goal, symptoms associated with psychiatric disorders may subside [17].

Arguments against using ACT in the pediatric population note that requisite concepts are too complex and abstract for children and adolescents to grasp. However, several reports note the successful application of ACT in the treatment of various pediatric populations [18-20]. Studies have also demonstrated that therapy based on mindfulness (which is a core component of ACT) is effective in reducing anxiety symptoms in children and adolescents [21,22]. Still, a dearth of empirical research has specifically examined ACT for pediatric anxiety disorders. In a case study, the anxiety and obsessive thoughts of an 18-year-old female with moderate mental retardation were treated with a 17-session ACT protocol that was modified for her developmental level [23]. Following treatment, the patient experienced decreased experiential avoidance, increased social confidence, and decreased duration of anxiety "episodes". Currently, a randomized controlled study is under way to examine the efficacy of ACT relative to CBT and wait-list control groups delivered via group therapy in the treatment of pediatric anxiety disorders [24]. This study will elucidate both the feasibility and efficacy of ACT in treating pediatric anxiety disorders and will help clinicians determine the best course of treatment for this population.

Attention bias modification

Attention biases toward threat-related stimuli are postulated to contribute to the etiology and maintenance of anxiety disorders [25,26]. Because of this, research has strived to implement ABM techniques to retrain attention biases away from threat. Most frequently, a computer-based dot-probe task is used, and the difference in response times in the identification of a visual probe when paired with threatening or neutral stimuli is used as the attention bias index [27,28]. Faster response times when the threatening stimuli are presented indicate an attention bias toward threat; these findings have been consistently demonstrated in both adults and children with anxiety [25,29,30]. ABM then implicitly retrains attention away from threatening stimuli by repeatedly presenting the visual probe over the neutral stimuli. Computerized ABM provides a systematic intervention that may be more palatable for youth who may find standard CBT or psychotherapy to be aversive.

Several studies have examined the efficacy of ABM in children with anxiety. In a study of chronically anxious children (mean age of 10 years), 2 sessions of ABM resulted in increased attention disengagement from threat, and anxious children were better able to shift their attention away from threatening stimuli [31]. In a randomized controlled trial (RCT) with clinically anxious children (ages 8 to 14 years) with primary separation anxiety, social phobia, or specific phobia, four sessions of ABM were successful in reducing clinician severity ratings of pediatric anxiety symptoms [32]. A case series reported downward trends of anxiety ratings from pre- to post-treatment following 8 sessions of ABM with anxious children who were deemed non-responders to a 12- to 14-week trial of CBT [33].

The clinical utility of ABM as an adjunct to CBT has also been examined. In a study of youth ages 13 to 17 years in a residential unit for severe anxiety, those who received ABM in addition to daily (weekday) CBT had significantly

greater reductions in anxiety symptoms at post-treatment relative to those who received CBT alone [34]. A recent RCT examined the efficacy of ABM-augmented CBT relative to placebo-augmented CBT and CBT monotherapy. Whereas both ABM and placebo groups showed significantly greater reductions in clinical ratings relative to the CBT-only group, only the active ABM group had significant reductions in parent- and self-rated anxiety measures [35].

Pharmacological interventions

Cognitive enhancers

Central glutamatergic systems have been implicated in the pathophysiology of various anxiety disorders [36]. *N*-methyl-D-aspartate (NMDA) subtype glutamate receptor-mediated facilitation in the basolateral amygdala has been suggested as a potential mechanism for the more rapid acquisition and retention of fear extinction. NMDA receptors have an established role in the induction of many forms of neuroplasticity best seen in long-term potentiation (LTP) [37-41]. In sum, glutamatergic activity at the NMDA receptor seems to be critically involved in the neural mechanisms of learning and memory [42]. Therefore, interest in pharmacological agents that target glutamatergic sites has increased in recent years.

Riluzole

Riluzole, an anti-glutamatergic agent, has been examined for its anxiolytic effects on anxiety disorders [43]. Several open-label trials in adults examining riluzole as monotherapy or an adjunct therapy have resulted in significant reductions in anxiety symptoms after treatment [44,45]. Among studies with youth, riluzole as an augmentation to pharmacotherapy was examined in a 12-week open-label study for children (ages 8 to 16 years) with treatment-resistant obsessive-compulsive disorder (OCD) [46]. At post-treatment, substantial OCD symptom reduction was found in 4 out of the 6 participants. However, a 12-week RCT of adjunctive riluzole among 60 treatment-resistant youth (ages 7 to 17 years old) with OCD failed to find significant differences between riluzole and placebo-augmented groups; however, this may be due to methodological limitations (e.g. sample characteristics and high rates of concomitant medications) [47]

D-cycloserine

In the treatment of specific anxiety disorders, particularly OCD, a core component of therapy is exposure and response prevention (E/RP). In E/RP, individuals are systematically exposed to fearful stimuli and prevented from engaging in unhelpful behaviors that will reduce anxiety (e.g. compulsions and avoidance behaviors). Repeated exposure to the fearful stimuli facilitates fear extinction, in which over time, the individual eventually experiences habituation (i.e. substantial decrease in anxiety by the end of the exposure) [48]. Although CBT with E/RP is a robust and efficacious treatment for pediatric OCD [49,50], recent studies have focused on ways to augment E/RP with DCS. DCS is an NMDA partial agonist that has been shown to enhance fear extinction learning in both animals and humans [51-53]. In adult trials, DCS demonstrated augmenting effects in the treatment of specific phobia of heights, social phobia, panic disorder, and OCD [54-59]. Additionally, DCS increased the overall speed of treatment effects; in a study of adults with OCD, those in the DCS group had reductions in symptoms six times faster in the first half of treatment relative to those who did not receive DCS [60].

In youth, only one published study has examined DCS as an adjunct to E/RP [61]. Amongst children with OCD (ages 8 to 17 years), no significant differences were found between the DCS-augmented E/RP group and the CBT-alone group; however, the DCS-augmented E/RP group showed small to moderate treatment effects (d = 0.31-0.47) on primary OCD outcome measures. Currently, a National Institute of Mental Health-funded multi-site study is being conducted to further examine the augmenting effects of DCS with E/RP in children with OCD. The study seeks to recruit 150 youth between the ages of 7 to 17 years and will provide important information regarding the incremental effectiveness of adjunctive DCS with E/RP in a pediatric population.

DCS is a well-tolerated pharmacological agent. Among the eight human studies using DCS as an adjunct to psychotherapy, there have been few to no adverse events [57,59,61,62]. Additionally, DCS may be particularly useful when rapid treatment gains are needed. Based on favorable findings in the literature, further research in the augmenting effects of DCS for behavioral treatment in other pediatric anxiety disorders is warranted.

Conclusions

Efficacious and safe methods of treatment are available for youth with anxiety disorders. However, a subset of children do not benefit from standard pharmacotherapy and behavioral interventions. Novel approaches are needed to provide alterative options for (partially) treatment-resistant youth, including pharmacological and non-pharmacological methods. Translational neuroscience is expected to open new avenues for treatment interventions in the next decade.

Abbreviations

ABM, attention bias modification; ACT, acceptance and commitment therapy; CBT, cognitive behavioral therapy;

DCS, d-cycloserine; E/RP, exposure and response prevention; NMDA, *N*-methyl-D-aspartate; OCD, obsessive-compulsive disorder; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor.

Disclosures

The authors declare that they have no disclosures.

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